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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/520,220 | 10/26/2005 | R .Rogers Yocum | BGI-154US2 | 2729 |

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| EXAMINER | |
|---|---|
| FRONDA, CHRISTIAN L | |
| **ART UNIT** | **PAPER NUMBER** |
| 1652 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
| 10/10/2008 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/520,220 | YOCUM ET AL. | |
| | Examiner | Art Unit | |
| | CHRISTIAN L. FRONDA | 1652 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *17 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-15,23,28,31-33 and 50-65* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15,23,28,31-33 and 50-65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 January 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/05,11/07,12/07,02/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

1. Applicants' arguments filed 09/17/2008 traversing the restriction requirement dated 03/17/2008 is acknowledged. Upon further consideration of applicants' arguments the restriction requirement dated 03/17/2008 has been withdrawn.

2. Claims 1-15, 23, 28, 31-33, and 50-65 are under consideration in this Office Action.

### *Claim Rejections - 35 U.S.C. § 112, 2nd Paragraph*

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-15, 23, 28, 31-33, and 50-65 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims encompass processes for enhanced production of pantothenate. However, the term "enhanced" is a relative term that renders the claims vague and indefinite. It is uncertain if "enhanced" production of pantothenate is compared to and based upon the amount of pantothenate produced by culturing an unmodified microorganism. Dependent claims 3-15, 23, 28, 31-33, and 50-65 are also rejected because they do not correct the defect of claims 1 or 2.

### *Claim Rejections - 35 U.S.C. § 112, 1st Paragraph*

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-15, 23, 28, 31-33, and 50-65 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants are directed toward the current USPTO Written Description Training Materials made available to the public on 04/11/2008 for information regarding examination of patent claims for compliance with the written description requirement of 35 U.S.C. 112, first paragraph.

The claims are genus claims encompassing processes for the enhanced production of pantothenate comprising culturing microorganisms having any deregulated genus of enzymes of the methylenetetrahydrofolate (MTF) biosynthetic pathway and/or any deregulated genus of enzymes of the pantothenate biosynthetic pathway. The scope of each genus includes many members with widely differing enzymatic activities, amino acid or nucleotide sequences, and/or structures, where each genus is highly variable because a significant number of structural and biological differences between genus members exists. The specification, however, does not describe and define any structural features, nucleotide and amino acid sequences, and/or biological functions that are commonly possessed by members of each genus.

The reference of Chica et al. (Curr Opin Biotechnol. 2005 Aug;16(4):378-84; PTO 892) teaches that the complexity of the structure/function relationship in enzymes has proven to be the factor limiting the general application of rational enzyme modification and design, where rational enzyme modification and design requires in-depth understanding of structure/function relationships. The reference of Sen et al. (Appl Biochem Biotechnol. 2007 Dec;143(3):212-23; PTO 892) teaches *in vitro* recombination techniques such as DNA shuffling, staggered extension process (StEP), random chimeragenesis on transient templates (RACHITT), iterative truncation for the creation of hybrid enzymes (ITCHY), recombined extension on truncated templates (RETT), and so on have been developed to mimic and accelerate nature's recombination strategy However, such directed evolution techniques only describes methods for searching and screening for enzymes with a desired property or properties.

The specification discloses a process for production of pantothenate comprising culturing a *Bacillus subtilis* host cell transformed with the plasmid pAN396 containing the glyA gene consisting of SEQ ID NO: 24 and the plasmid pAN824 containing the serA gene consisting of SEQ ID NO: 31.

MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In this case, the specification fails to disclose additional microorganisms with deregulated MTF and pantothenate biosynthetic pathways as encompassed by the claims. As such the disclosure of the above mentioned *Bacillus subtilis* host cell transformed with the plasmid pAN396 containing the glyA gene consisting of SEQ ID NO: 24 and the plasmid pAN824 containing the serA gene consisting of SEQ ID NO: 31 is insufficient to be representative of the attributes and features common to all the members of each claimed genus.

Furthermore, the specification dos not provide a correlation between any structure of any enzyme of the MTF and pantothenate biosynthetic pathways and pantothenate production based on which those of ordinary skill in the art could predict which enzyme in these pathways can be deregulated in any microorganism that will result in enhanced pantothenate production. Further, there is no art-recognized correlation between any structure of any enzyme of the MTF and pantothenate biosynthetic pathway and pantothenate production based on which those of ordinary skill in the art could predict which enzyme can be deregulated in these pathways in any microorganism that will result in enhanced pantothenate production. Consequently, there is no information about which enzyme of the MTF and pantothenate biosynthetic pathways that can be deregulated in any microorganism that will result in enhanced pantothenate production.

*Vas-Cath, Inc. v. Mahurkar,* 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d

1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class, where the specification provided only the bovine sequence.

In view of the above considerations, one of skill in the art would not recognize that applicants were in possession of each claimed genus.

7. Claims 1-15, 23, 28, 31-33, and 50-65 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a process for production of pantothenate comprising culturing a *Bacillus subtilis* host cell transformed with the plasmid pAN396 containing the glyA gene consisting of SEQ ID NO: 24 and the plasmid pAN824 containing the serA gene consisting of SEQ ID NO: 31; does not reasonably provide enablement for any other embodiment as recited in the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims..

According to MPEP 2164.01(a), factors considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

MPEP§ 2164.04 states that while the analysis and conclusion of a lack of enablement are based on the factors discussed in MPEP § 2164.01(a) and the evidence as a whole, it is not necessary to discuss each factor in the written enablement rejection. The language should focus on those factors, reasons, and evidence that lead the examiner to conclude that the specification fails to teach how to make and use the claimed invention without undue experimentation, or that the scope of any enablement provided to one skilled in the art is not commensurate with the

scope of protection sought by the claims. Accordingly, the factors most relevant to the instant rejection are addressed in detail below.

The nature and breadth of the claims encompass any processes for the enhanced production of pantothenate comprising culturing microorganisms having any deregulated enzymes of the MTF biosynthetic pathway and/or any deregulated of enzymes of the pantothenate biosynthetic pathway.

The reference of Chica et al. (Curr Opin Biotechnol. 2005 Aug;16(4):378-84; PTO 892) teaches that the complexity of the structure/function relationship in enzymes has proven to be the factor limiting the general application of rational enzyme modification and design, where rational enzyme modification and design requires in-depth understanding of structure/function relationships. The reference of Sen et al. (Appl Biochem Biotechnol. 2007 Dec;143(3):212-23) teaches *in vitro* recombination techniques such as DNA shuffling, staggered extension process (StEP), random chimeragenesis on transient templates (RACHITT), iterative truncation for the creation of hybrid enzymes (ITCHY), recombined extension on truncated templates (RETT), and so on have been developed to mimic and accelerate nature's recombination strategy However, such directed evolution techniques only enable methods for searching and screening for enzymes with a desired property or properties.

The specification provides guidance, prediction, and working examples for a process for production of pantothenate comprising culturing a *Bacillus subtilis* host cell transformed with the plasmid pAN396 containing the glyA gene consisting of SEQ ID NO: 24 and the plasmid pAN824 containing the serA gene consisting of SEQ ID NO: 31. The specification, however, does not provide guidance, prediction, and working examples for making the scope of the entire invention as claimed.

The specification dos not provide a correlation between any structure of any enzyme of the MTF and pantothenate biosynthetic pathways and pantothenate production based on which those of ordinary skill in the art could predict which enzyme in these pathways can be deregulated in any microorganism that will result in enhanced pantothenate production. Further, there is no art-recognized correlation between any structure of any enzyme of the MTF and pantothenate biosynthetic pathway and pantothenate production based on which those of ordinary skill in the art could predict which enzyme can be deregulated in these pathways in any

microorganism that will result in enhanced pantothenate production. Consequently, there is no information about which enzyme of the MTF and pantothenate biosynthetic pathways that can be deregulated in any microorganism that will result in enhanced pantothenate production.

Thus, an undue amount of trial and error experimentation must be preformed where such experimentation involves searching and screening a vast number of biological sources for enzyme of the MTF and pantothenate biosynthetic pathway, deregulating the enzyme by any genetic modification, and determining if such deregulation of the enzyme will result in enhanced production of pantothenate in any microorganism. General teaching regarding screening and searching for the claimed invention is not guidance for making the claimed invention.

Therefore, in view of the overly broad scope of the claims, the specification's lack of specific guidance and prediction, the specification's lack of additional working examples, and the amount of experimentation required; it would require undue experimentation for a skilled artisan to make and use the claimed invention. Without sufficient guidance, the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988).

***Conclusion***

8. No claim is allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christian L Fronda whose telephone number is (571)272-0929. The examiner can normally be reached Monday-Thursday and alternate Fridays between 9:00AM - 5:00PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nashaat Nashed can be reached on (571)272-0934. The fax phone number for the organization where this application or proceeding is assigned is (571)273-8300.

10. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications

may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Christian L. Fronda/
Primary Examiner
Art Unit 1652